

PARTNERSHIP COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)Date of mailing (day/month/year)
09 April 1999 (09.04.99)To:
United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

International application No.
PCT/EP98/04219Applicant's or agent's file reference
PHA 1776International filing date (day/month/year)
02 July 1998 (02.07.98)Priority date (day/month/year)
21 July 1997 (21.07.97)

Applicant

SOEGAARD, Morten et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

12 February 1999 (12.02.99)



in a notice effecting later election filed with the International Bureau on:

2. The election was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Nicola Wolff

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 17 January 2000 (17.01.00)
Applicant's or agent's file reference PHA 1776
International application No. PCT/EP98/04219

From the INTERNATIONAL BUREAU

To:

MAZZINI, Giuseppe
Pharmacia & Upjohn S.p.A.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

1. The following indications appeared on record concerning:				
<input checked="" type="checkbox"/> the applicant <input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative				
Name and Address DOHLSTEN, Mikael Gerdagatan 12B S-223 62 Lund Sweden	State of Nationality		State of Residence	
	SE		SE	
	Telephone No.			
	Facsimile No.			
Name and Address DOHLSTEN, Mikael Carl Skottsbergs gata 10 S-413 19 Goteborg Sweden	Telephone No.		Teleprinter No.	
	Facsimile No.			
	Teleprinter No.			
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:				
<input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence				
Name and Address DOHLSTEN, Mikael Carl Skottsbergs gata 10 S-413 19 Goteborg Sweden	State of Nationality		State of Residence	
	SE		SE	
	Telephone No.			
	Facsimile No.			
Name and Address DOHLSTEN, Mikael Carl Skottsbergs gata 10 S-413 19 Goteborg Sweden	Facsimile No.		Teleprinter No.	
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input type="checkbox"/> the International Preliminary Examining Authority		<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Eugénia Santos Telephone No.: (41-22) 338.83.38
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Pharmacia & Upjohn S.p.A.
BREVETTI

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23 APR 1999

PRESENT COOPERATION TREATY

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

MAZZINI, Giuseppe
Pharmacia & Upjohn S.p.A.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 09 April 1999 (09.04.99)	
Applicant's or agent's file reference PHA 1776	
International application No. PCT/EP98/04219	International filing date (day/month/year) 02 July 1998 (02.07.98)
Priority date (day/month/year) 21 July 1997 (21.07.97)	
Applicant PHARMACIA & UPJOHN AB et al	

IMPORTANT INFORMATION

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
National :AU,BG,BR,CA,CN,CZ,IL,JP,KR,NO,NZ,PL,RO,US
2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
National :HU,ID,MX,SG,SI,UA
3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until **31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Nicola Wolff Telephone No. (41-22) 338.83.38
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PATENT COOPERATION TREATY

Pharmacia & Upjohn S.p.A.
BREVETTI

R 15 FEB 1999 PCT
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NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

MAZZINI, Giuseppe
Pharmacia & Upjohn S.p.A.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year)
04 February 1999 (04.02.99)

Applicant's or agent's file reference
PHA 1776

IMPORTANT NOTICE

International application No.
PCT/EP98/04219

International filing date (day/month/year)
02 July 1998 (02.07.98)

Priority date (day/month/year)
21 July 1997 (21.07.97)

Applicant
PHARMACIA & UPJOHN AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, BR, CN, EP, IL, JP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

BG, CA, CZ, EA, HU, ID, MX, NO, NZ, PL, RO, SG, SI, UA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 04 February 1999 (04.02.99) under No. WO 99/04820

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

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PATENT COOPERATION TREATY

PCT

REC'D 29 OCT 1999
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PHA 1776	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP98/04219	International filing date (day/month/year) 02/07/1998	Priority date (day/month/year) 21/07/1997
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant PHARMACIA & UPJOHN AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 12/02/1999	Date of completion of this report 27.10.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gore, V Telephone No. +49 89 2399 8590



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/04219

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-75 as originally filed

Claims, No.:

1-34 as originally filed

Drawings, sheets:

1-15 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.
 claims Nos. 1-15.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/04219

the said international application, or the said claims Nos. 1-15 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

restricted the claims.
 paid additional fees.
 paid additional fees under protest.
 neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

complied with.
 not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

all parts.
 the parts relating to claims Nos. .

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/04219

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-15,21-23,33
	No:	Claims 16-20,24-32,34
Inventive step (IS)	Yes:	Claims 1-15,21-23,33
	No:	Claims 16-20,24-32,34
Industrial applicability (IA)	Yes:	Claims 16-34 (YES), 1-15 see separate sheet
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Reference is made to the following documents :

D1 : WO-A-9736932

D2 : Immunology Today vol.18 No.8 (08.1997), pages 379-386.

D3 : WO-A-9826747

D4 : WO-A-9845325

D5 : Immunotechnology vol.2 No.3 (1996), pages 151-162.

D6 : J. Clin. Oncol. vol.15 No.5 (05.1997), pages 1994-2007.

D7 : Eur. J. Immunol.

D8 : Int. J. Cancer, vol.68 (1996), pages 109-113.

D9 : Eur. J. Haematol., vol.60 No.4 (1998), pages 233-239.

D10 : WO-A-9601650

D11 : WO-A-9324136

D12 : Proc. Nat. Acad. Sci. USA, vol.94 No.6 (1997), pages 2489-2494.

D13 : J. Immunol. Meth., vol.204 No.1 (1998), pages 33-41.

D14 : US-A-5635599

D15 : WO-A-9530015

D16 : US-A-5541087

Regarding point III

2. Claims 1-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Regarding point IV

3. The Examiner, partly following the International Searching Authority, considers that the present application contains four inventions, namely :

A) Method for inactivating a target cell in the presence of T cells by using a superantigen in the presence of an immunomodulator wherein at least one of them is conjugated to a targeting moiety (claims 1-15)

B) Superantigen conjugates (including fusion proteins) comprising a targeting moiety a superantigen and an immune modulator (claims 16-26 and parts of claims 8-15)

C) Targeted immunomodulator comprising a conjugate between a targeting moiety

and a non-superantigen immune modulator (claims 27-30)

D) DNA molecule encoding a superantigen and an immune modulator (claims 31-34 and parts of claims 9-15).

The problem underlying the present invention is the improvement on methods of inactivation of targeted cancer cells in the present of T lymphocytes. The proposed solutions consist compositions comprising a superantigen and an immune modulator where at least one of the two is in the form of a conjugate to a targeting moiety, including : triple conjugates, double conjugates, fusion proteins and also the elements in a free form. The concept linking these solutions is the use of a superantigen in the presence of a immune modulator where at least one of them is in the form of a conjugate with a targeting moiety.

Prior art documents disclose some of the solutions to the problem proposed by the applicant (see point V below). The idea of providing a composition comprising a superantigen conjugated to an antibody is known (see point V below), and cannot serve as a single general inventive concept linking the individual subjects in which the application has been divided.

It may be argued that the technical problem underlying the present invention is solved by the administration of a superantigen in combination with an immune modulator. However, this seems to be in contradiction with the formulation of claim 1 where the superantigen + immune modulator combination is mentioned in the first part of the claim, and not in the characterizing part, implicitly recognizing that this combination is known in the prior art. Moreover, a composition comprising a combination of a superantigen and an immune modulator is disclosed in a prior art document cited in the search report (see D14) and thus cannot serve as a general inventive concept.

In conclusion, the application lacks unity of invention.

Regarding point VI

4. The present opinion is based on the assumption that the priority claimed by the present application is valid. Should it not be the case, D2 would also be considered as part of the prior art in the international and regional phases.

D1 and D3 cannot be regarded as available prior art in the international phase but could be taken into account for the assessment of novelty in the regional phase in EPC countries. D4 could also be considered as prior art in the regional phase.

Regarding point VIII

5. Claim 1 as a whole is not clear because "at least one of the superantigen (SAG) and the immune modulator (IM) is in the form of a conjugate between a free SAG and a targeting moiety(T)" does not make sense. An immune modulator cannot be in the form of a SAG-T conjugate. What is probably meant is that at least one of the SAG and the IM is conjugated to a T, as outlined in the description page 7 lines 8-11 and 22-25.

It follows that dependent claim 2 is also unclear, since embodiment e) of claim 2 features SAG-IM conjugates that do not contain a T. This embodiment does not fall within the scope of claim 1 and is in contradiction with the statements of page 7 of the description. The same is true for independent claims 16 and 27, which are directed to SAG-IM conjugates in the embodiments where $x=0$.

Claim 6, depending from claim 2, mentions the T moiety of embodiment e) of claim 2 whereas this embodiment is directed to a SAG-IM conjugate. Moreover, claim 8 is itself dependent from claim 6 and relates to specific targeting moieties. Similarly, claim 26 should not be dependent from claims 24-25 because there is no T in the embodiments of cl.24-25. These claims are therefore also unclear.

5.1 In claim 11, the expression "for instance...CD86" is not limiting the scope of the claim (see the PCT Guidelines III 4.6). The part of the claim that can be regarded as a limiting technical feature is the expression "extracellular parts of lymphocyte surface bound receptors and ligands", which is too broad to allow the person skilled in the art to determine unambiguously which compounds fall under the scope of the claim. The latter comment can also be applied to claim 12, in which the only characterizing technical feature is formulated as a result to be achieved and is too vague to define the scope of the claim properly.

5.2 Claims 19-23 are all directly or indirectly dependent from claims 16-18. However, cl.19-23 are directed to "a fusion protein" whereas cl.16-18 relate to "a superantigen conjugate". For the sake of clarity, cl.19-23 should thus be reformulated.

5.3 Claim 25 should be dependent from claim 24, not from claim 16.

Regarding point V

6. For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims

to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7. **D5** is a review article dealing with antibody-targeted SAGs in cancer immunotherapy. The expression of a C215Fab-SEA conjugate (a T-SAG conjugate, SEA meaning Staphylococcal enterotoxin A), which is the transcription product of a bicistronic mRNA, in *E.coli* is described, as well as its antitumor effects *in vivo* in mice (see fig.6). The SAG is conjugated to the C215Fab targeting moiety via a Gly-Gly-Pro tripeptide linker (see fig.3). The C215Fab-SEA_{D227A} conjugate had a lower affinity for MHC class II molecules while retaining TCR binding abilities and exhibited lower toxicity than C215Fab-SEA (see pages 159-160 and fig.8).

D6 describes a phase I trial for therapy of colorectal cancer in human patients with a C242Fab-SEA conjugate.

D7 describes similar tests with the same conjugate in SCID mice.

D8 discloses the antitumoral properties of C215Fab-SEA conjugates in mice with lung metastases of melanoma (see abstract). It strongly suggests that the efficacy of this therapy is partly due to the stimulation of IFN- γ production by CD4+ cells by the C215Fab-SEA conjugate (see last § of the discussion).

D9 discloses antibody-directed superantigen-mediated T cell killing of myeloid leukaemic cell lines. In this experiment, leukaemic cells were killed after being contacted *in vitro* with T cells and PA-SEA_{D227A} conjugate (PA=protein A, a protein binding to the Fc region of antibodies). The construction of a PA-SEA_{D227A} fusion protein and its testing as a candidate drug for therapy of myeloid leukaemias is suggested (see page 2034 left col. and abstract).

D10 claims a conjugate comprising : a) a targeting moiety, and

b) a peptide containing an aminoacid (aa) sequence derived from a SAG and having a modified ability to bind to MHC class II but retains TCR V β binding ability.

A method for the lysis of mammalian cells (in an embodiment, cancer cells) in which said cells are contacted with T lymphocytes and a conjugate as defined above (see abstract and claims 10-12).

In **D11**, a method of treating cancer in a patient is disclosed, which comprises administering to a host a staphylococcal enterotoxin in combination with a cytokine (e.g. IL, IFN...) *in vitro* to induce T lymphocyte proliferation, said T cells being subsequently administered to the tumor-bearing patient (see cl.14, 24, 26 and 33).

D12 describes the antitumoral properties of Fab-SEA and Fab-SEA_{D227A} in mice with melanoma tumors, the second conjugate showing a markedly reduced toxicity in comparison with the first one (see abstract).

D13 describes conjugates comprising SEA linked to gVIIIp protein (a phage coat protein) via a peptide linker. This conjugate is used for screening and expression of

enterotoxins in phage libraries (see abstract).

D14 is directed to fusion proteins comprising IL-2 (see cl.9) and in particular fusion proteins comprising IL-2 and a modified pseudomonas enterotoxin or a diphtheria toxin (DT) (cl.10). Examples 4 and 5 also disclose the following conjugates comprising an immunomodulator and a SAG : IL4-DT, IL2-DT. The conjugate of example 3 is the antibody-cytokine conjugate B₃(Fv)-IL4(38-37).

In **D15**, a fusion protein comprising an Epstein-Barr virus superantigen (BZLF2) and the Fc domain of an antibody is used for treating or preventing immune or inflammatory responses (see abstract, page 26 and cl.13-15).

In **D16**, expression vectors are described that allow the expression of a protein of interest fused to the Fc domain of an antibody (see abstract). An example of such a fusion protein is IL2-Fc (ex.5).

7.1 Assuming that embodiment e) of dependent claim 2 is not within the scope of claim 1 and that claim 1 is formulated clearly (see point 3 above), none of the available prior art document does disclose a method for inactivating target cells comprising contacting said cells with T cells in the presence of a SAG and an IM, at least one of SAG or IM being conjugated to a T. The subject-matter of claims 1-15 would thus be new.

7.2 Claim 16 is directed to a conjugate of the formula : (T)x(SAG)y(IM)z wherein y>0 and at least one of x and z >0. The components are linked together via organic linker(s).

When z=0, the claimed conjugate is T-SAG (x=y=1). All documents D5 to D13 and D15 disclose a T-SAG conjugate. In most of these documents, the conjugate is a fusion protein.

When x=0 and y=z=1, claim 16 is directed to a SAG-IM conjugate. SAG-IM fusion proteins are described in D14. In conclusion, claims 16-18, as well as cl.24-25 (directed to SAG-IM conjugates) would not be new over D5-D15.

7.3 In most of the above documents, the targeting moiety T is an Ab or a fragment thereof. Some of D5-D15 also discloses superantigens that have been modified according to cl.9-10 of the present application, for instance C215Fab-SEA_{D227A} in D5 or C242Fab-SEA_{D227A} in D6. Claims 19-20 and 26 do not seem novel.

7.4 Claim 27 is directed to a conjugate of the formula : (T)x(SAG)y(IM)z wherein z>0 and at least one of x and y >0. The components are linked together via organic linker(s).

When x=0 and y=z=1, claim 27 is directed to a SAG-IM conjugate, which does not seem to be new (see point 5.2 above).

When y=0 and x=z=1, the claimed conjugate is T-IM. D16 discloses an IL2-Fc fusion protein and would thus destroy the novelty of this embodiment.

It follows that claims 27-30 would not be novel.

7.5 D14 discloses a bicistronic DNA molecule encoding a SAG-IM fusion protein. Claims 31-32 and 24 do not appear to be novel.

7.6 Claims 21-23 and 33 are directed to a triple conjugate T-SAG-IM and a DNA molecule encoding such a triple conjugate. No T-SAG-IM triple conjugate has been disclosed previously, so that dependent claims 21-23 and 33 seem to be novel.

8. Either D5 or D10 can be considered as the closest prior art. They both disclose the use of targeted superantigens (SAG-T) together with T cells for treating tumors. The superantigen moiety is preferably modified so as to retain TCR binding ability but with lower affinity for MHC class II molecules. None of these documents does suggest to use an immunomodulator in combination with the T-SAG.

D8 partly elucidates the mechanism of action of C215Fab-SEA conjugates that leads to destruction of melanoma cells. The stimulation of the production of immune modulators such as IL-2 and IFN- γ by CD4+ cells seems to play a role in this process, but the co-administration of an immune modulator and a targeted superantigen is not suggested.

On the other hand, D11 describes a method for treating cancer comprising contacting T cells with tumor cells in the presence of a staphylococcal enterotoxin and a cytokine, and administering said T cells to a tumor-bearing patient. The combination of SAG and IM is thus disclosed in the same context as in the present application (SAG dependent cellular cytotoxicity for treating cancer) but it is not suggested that this method may advantageously be improved by conjugating at least one of SAG or IM to a targeting moiety. It does not seem obvious for the person skilled in the art to combine D5 (or D10) to D11 in order to solve the four technical problems mentioned on pages 6-7 of the present application.

For the same reason, a triple conjugate T-SAG-IM could also be regarded as non-obvious.

Consequently, claims 1-15, 21-23 and 33 would appear to involve an inventive step.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04219

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K47/48 A61K39/085 A61K39/385 C07K14/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SØGAARD M ET AL: "Antibody-targeted superantigens in cancer immunotherapy" IMMUNOTECHNOLOGY, vol. 2, no. 3, September 1996, page 151-162 XP004070290 see fig 1 and 6 in colour see figures 3,4,8 see page 160 see page 154 - page 158 --- -/-</p>	1-34



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

9 February 1999

Date of mailing of the international search report

26.03.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
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Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/04219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WOODLAND D L ET AL: "Why do superantigens care about peptides?" IMMUNOLOGY TODAY, vol. 18, no. 1, January 1997, page 18-22 XP004016757 see fig 1, table 1 in colour see page 20, column 2 ---	1-34
Y,P	SILVERMAN G J: "B-cell superantigens" IMMUNOLOGY TODAY, vol. 18, no. 8, August 1997, page 379-386 XP004084830 see page 382, column 2, paragraph 2 ---	1-34
X	WO 93 24136 A (TERMAN DAVID S ;STONE JAY L (US)) 9 December 1993 see abstract; claim 38 see page 55, line 30-35; claims 14-16,24,26,33 ---	1-34
Y,P	WO 98 26747 A (TERMAN DAVID S) 25 June 1998 see abstract see page 62-63; tables 3,7 see page 44 ---	1-15
A	US 5 545 716 A (JOHNSON HOWARD M ET AL) 13 August 1996 see abstract ---	1-15
X	HANSSON J ET AL: "Genetically engineered superantigens as tolerable antitumor agents." PROC NATL ACAD SCI U S A, MAR 18 1997, 94 (6) P2489-94, XP002092807 UNITED STATES see abstract; figure 1 see discussion see page 2490, column 1, paragraph 3 ---	1-34
X	WUNG J L ET AL: "Selection of phage-displayed superantigen by binding to cell -surface MHC class II" JOURNAL OF IMMUNOLOGICAL METHODS, vol. 204, no. 1, 12 May 1997, page 33-41 XP004107714 see the whole document ---	1-34
X	MUNSON, SIBYL H. ET AL: "Identification and characterization of staphylococcal enterotoxin types G and I from <i>Staphylococcus aureus</i> " INFECT. IMMUN. (1998), 66(7), 3337-3348 CODEN: INFIBR;ISSN: 0019-9567, XP002092808 see the whole document ---	1-34

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GIANTONIO BJ ET AL: "Superantigen-based immunotherapy: a phase I trial of PNU-214565, a monoclonal antibody-staphylococcal enterotoxin A recombinant fusion protein, in advanced pancreatic and colorectal cancer." J CLIN ONCOL, MAY 1997, 15 (5) P1994-2007, XP002084828</p> <p>UNITED STATES see discussion see abstract</p> <p>---</p>	1-34
X	<p>LITTON M J ET AL: "ANTIBODY-TARGETED SUPERANTIGEN THERAPY INDUCES TUMOR-INFILTRATING LYMPHOCYTES, EXCESSIVE CYTOKINE PRODUCTION, AND APOPTOSIS IN HUMAN COLON CARCINOMA" EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 26, no. 1, January 1996, pages 1-9, XP002050535</p> <p>see page 6 - page 7</p> <p>---</p>	1-34
X	<p>ROSENDAHL A. ET AL: "Immune response during tumor therapy with antibody-superantigen fusion proteins" INT. J. CANCER, vol. 68, 1996, pages 109-113, XP002084829</p> <p>see abstract see page 112, column 2, paragraph 4</p> <p>---</p>	1-34
X	<p>GIDLÖF, CECILIA ET AL: "Antibody-directed superantigen-mediated T-cell killing of myeloid leukemic cell line cells" EUR. J. HAEMATOL. (1998), 60(4), 233-239</p> <p>CODEN: EJHAEC; ISSN: 0902-4441, XP002084830</p> <p>see discussion</p> <p>---</p>	1-34
X, P	<p>WO 97 36932 A (KALLAND TERJE ;PHARMACIA & UPJOHN AB (SE); ANTONSSON PER (SE); HAN) 9 October 1997</p> <p>cited in the application see the whole document</p> <p>---</p>	1-34
X	<p>WO 96 01650 A (KALLAND TERJE ;ABRAHMSSEN LARS (SE); BJOERK PER (SE); DOHLSTEN MIKA) 25 January 1996</p> <p>cited in the application see the whole document</p> <p>---</p> <p>-/-</p>	1-34

INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/EP 98/04219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 45325 A (UNIV ROCKEFELLER) 15 October 1998 see abstract ---	1-34
X	US 5 635 599 A (PASTAN IRA H ET AL) 3 June 1997 see claims 9,10; examples 3-5 ---	1-34
X	WO 95 30015 A (UNIV MISSOURI ;IMMUNEX CORP (US); NAT INST HEALTH (US)) 9 November 1995 see abstract ---	1-34
X	WO 96 36366 A (DOW STEVE W ;ELMSLIE ROBYN E (US); NAT JEWISH CENTER FOR IMMUNOLO) 21 November 1996 see abstract ---	1-34
X	US 5 541 087 A (LO KIN-MING ET AL) 30 July 1996 see abstract -----	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04219

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9736932	A 09-10-1997	AU 2525197	A	22-10-1997	
		CA 2222757	A	09-10-1997	
		CZ 9703712	A	13-05-1998	
		EP 0835266	A	15-04-1998	
		NO 975435	A	29-01-1998	
		PL 323626	A	14-04-1998	
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WO 9601650	A 25-01-1996	AU 699147	B	26-11-1998	
		AU 2994095	A	09-02-1996	
		CA 2194673	A	25-01-1996	
		CN 1152877	A	25-06-1997	
		EP 0766566	A	09-04-1997	
		FI 970100	A	10-01-1997	
		HU 77257	A	02-03-1998	
		NO 970108	A	20-02-1997	
		NZ 289951	A	23-12-1998	
		PL 318162	A	26-05-1997	
		SE 9402430	A	12-01-1996	
		ZA 9505746	A	20-02-1996	
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WO 9324136	A 09-12-1993	AU 4526593	A	30-12-1993	
		WO 9420124	A	15-09-1994	
		US 5728388	A	17-03-1998	
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WO 9826747	A 25-06-1998	NONE			
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US 5545716	A 13-08-1996	US 5859207	A	12-01-1999	
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WO 9845325	A 15-10-1998	AU 6950198	A	30-10-1998	
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US 5635599	A 03-06-1997	AU 694211	B	16-07-1998	
		AU 2285795	A	30-10-1995	
		CA 2187283	A	19-10-1995	
		EP 0754192	A	22-01-1997	
		WO 9527732	A	19-10-1995	
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WO 9530015	A 09-11-1995	AU 2370595	A	29-11-1995	
		US 5726286	A	10-03-1998	
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WO 9636366	A 21-11-1996	US 5705151	A	06-01-1998	
		AU 5801696	A	29-11-1996	
		CA 2221305	A	21-11-1996	
		EP 0850071	A	01-07-1998	
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US 5541087	A 30-07-1996	AU 691980	B	28-05-1998	
		AU 3676595	A	29-03-1996	
		CA 2199830	A	21-03-1996	
		EP 0782625	A	09-07-1997	
		JP 10505751	T	09-06-1998	
		WO 9608570	A	21-03-1996	
		US 5726044	A	10-03-1998	
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/04219

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-15 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 98/04219

International Application No.

02.07.98

02 JUL 1998

International Filing Date

EUROPEAN PATENT OFFICE

PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

PHA 1776

Box No. I TITLE OF INVENTION

DIRECTED CYTOLYSIS OF TARGET CELLS, AGENTS AND COMPOSITIONS CAUSING CYTOLYSIS, AND COMPOUNDS THAT CAN BE USED TO PRODUCE THE AGENTS

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

PHARMACIA & UPJOHN AB
S-112 87 Stockholm
Sweden

This person is also inventor.

Telephone No.

0046 18 16 3000

Facsimile No.

0046 18 12 6077

Teleprinter No.

State (i.e. country) of nationality:

SE

State (i.e. country) of residence:

SE

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

SOEGAARD Morten
Rysensteensgade 16
DK-1564 Kopenhagen
Denmark

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

DK

State (i.e. country) of residence:

DK

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box for the purposes of:

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

agent

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Giuseppe Mazzini
PHARMACIA & UPJOHN S.p.A.
Viale Pasteur, 10
20014 Nerviano (Milano)
Italy

Telephone No.

+39+02+4838.5415

Facsimile No.

+39+02+4838.5397

Teleprinter No.

Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

ABRAHMSSEN Lars
Lillangsgatan 28
168 58 Bromma
Sweden

This person is:

applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

SE

State (i.e. country) of residence:

SE

This person is applicant for the purposes of:

 all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

LANDO Peter
Carl Gustavs vag 26 A
211 46 Malmo
Sweden

This person is:

applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

SE

State (i.e. country) of residence:

SE

This person is applicant for the purposes of:

 all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

FORSBERG Göran
Kulgränden 15A
S-226 49 Lund
Sweden

This person is:

applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

SE

State (i.e. country) of residence:

SE

This person is applicant for the purposes of:

 all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

KALLAND Terje
Domberrevagen 4
246 32 Loddekoinge
Sweden

This person is:

applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

NO

State (i.e. country) of residence:

SE

This person is applicant for the purposes of:

 all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:

in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America;
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part";
- (vi) if there are more than three earlier applications whose priority is claimed;

in such case, write "Continuation of Box No." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;

in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below;

in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.

Continuation of Box No. III

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

DOHLSTEN Mikael
Gerdagatan 12B
223 62 Lund
Sweden

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality: SE

State (i.e. country) of residence: SE

This person is applicant for the purposes of:

all designated States

all designated States except the United States of America

the United States of America only

the States indicated in the Supplemental Box

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

<input type="checkbox"/> AL Albania	<input type="checkbox"/> LT Lithuania
<input type="checkbox"/> AM Armenia	<input type="checkbox"/> LU Luxembourg
<input type="checkbox"/> AT Austria	<input type="checkbox"/> LV Latvia
<input checked="" type="checkbox"/> AU Australia	<input type="checkbox"/> MD Republic of Moldova
<input type="checkbox"/> AZ Azerbaijan	<input type="checkbox"/> MG Madagascar
<input type="checkbox"/> BA Bosnia and Herzegovina	<input type="checkbox"/> MK The former Yugoslav Republic of Macedonia
<input type="checkbox"/> BB Barbados	<input type="checkbox"/>
<input checked="" type="checkbox"/> BG Bulgaria	<input type="checkbox"/> MN Mongolia
<input checked="" type="checkbox"/> BR Brazil	<input type="checkbox"/> MW Malawi
<input type="checkbox"/> BY Belarus	<input checked="" type="checkbox"/> MX Mexico
<input checked="" type="checkbox"/> CA Canada	<input checked="" type="checkbox"/> NO Norway
<input type="checkbox"/> CH and LI Switzerland and Liechtenstein	<input checked="" type="checkbox"/> NZ New Zealand
<input checked="" type="checkbox"/> CN China	<input type="checkbox"/> PL Poland
<input type="checkbox"/> CU Cuba	<input type="checkbox"/> PT Portugal
<input checked="" type="checkbox"/> CZ Czech Republic	<input checked="" type="checkbox"/> RO Romania
<input type="checkbox"/> DE Germany	<input type="checkbox"/> RU Russian Federation
<input type="checkbox"/> DK Denmark	<input type="checkbox"/> SD Sudan
<input type="checkbox"/> EE Estonia	<input type="checkbox"/> SE Sweden
<input type="checkbox"/> ES Spain	<input checked="" type="checkbox"/> SG Singapore
<input type="checkbox"/> FI Finland	<input checked="" type="checkbox"/> SI Slovenia
<input type="checkbox"/> GB United Kingdom	<input type="checkbox"/> SK Slovakia
<input type="checkbox"/> GE Georgia	<input type="checkbox"/> SL Sierra Leone
<input type="checkbox"/> GH Ghana	<input type="checkbox"/> TJ Tajikistan
<input type="checkbox"/> GM Gambia	<input type="checkbox"/> TM Turkmenistan
<input type="checkbox"/> GW Guinea-Bissau	<input type="checkbox"/> TR Turkey
<input checked="" type="checkbox"/> HU Hungary	<input type="checkbox"/> TT Trinidad and Tobago
<input checked="" type="checkbox"/> ID Indonesia	<input checked="" type="checkbox"/> UA Ukraine
<input checked="" type="checkbox"/> IL Israel	<input type="checkbox"/> UG Uganda
<input type="checkbox"/> IS Iceland	<input checked="" type="checkbox"/> US United States of America
<input checked="" type="checkbox"/> JP Japan	<input type="checkbox"/>
<input type="checkbox"/> KE Kenya	<input type="checkbox"/>
<input type="checkbox"/> KG Kyrgyzstan	<input type="checkbox"/>
<input type="checkbox"/> KP Democratic People's Republic of Korea	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> KR Republic of Korea	<input type="checkbox"/>
<input type="checkbox"/> KZ Kazakhstan	<input type="checkbox"/>
<input type="checkbox"/> LC Saint Lucia	<input type="checkbox"/>
<input type="checkbox"/> LK Sri Lanka	<input type="checkbox"/>
<input type="checkbox"/> LR Liberia	<input type="checkbox"/>
<input type="checkbox"/> LS Lesotho	<input type="checkbox"/>

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

.....

.....

.....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM

Further priority claims are indicated in the Supplemental Box

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) US [United States]	21.07.1997 (July 21, 1997)	60/053,211	
item (2) Sweden	14.11.1997 (November 14, 1997)	9704170-1	
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA /

Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office): Date (day/month/year): Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 5 sheets
2. description	: 65 sheets
3. claims	: 9 sheets
4. abstract	: 1 sheets
5. drawings	: 25 sheets
Total	: 105 sheets

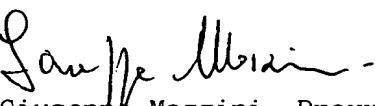
This international application is accompanied by the item(s) marked below:

1. <input checked="" type="checkbox"/> separate signed power of attorney (inventors)	5. <input checked="" type="checkbox"/> fee calculation sheet
2. <input checked="" type="checkbox"/> copy of general power of attorney	6. <input type="checkbox"/> separate indications concerning deposited microorganisms
3. <input type="checkbox"/> statement explaining lack of signature	7. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette)
4. <input checked="" type="checkbox"/> priority document(s) identified in Box No. VI as item(s):	8. <input checked="" type="checkbox"/> other (specify): (accompanying letter)

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



Giuseppe Mazzini, Proxy, G.A. 38543

For receiving Office use only	
1. Date of actual receipt of the purported international application:	02.07.98
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	02 JUL 1998
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid
For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	
2. Drawings:	
<input checked="" type="checkbox"/> received: <input type="checkbox"/> not received:	

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

PATENT COOPERATION TREATY

FT/PV

PCT

**NOTIFICATION OF RECEIPT OF
RECORD COPY**

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

MAZZINI, Giuseppe
Pharmacia & Upjohn S.p.A.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 13 August 1998 (13.08.98)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PHA 1776	International application No. PCT/EP98/04219

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

PHARMACIA & UPJOHN AB (for all designated States except US)
SOEGAARD, Morten et al (for US)

International filing date : 02 July 1998 (02.07.98)
Priority date(s) claimed : 21 July 1997 (21.07.97)
Priority date(s) claimed : 14 November 1997 (14.11.97)

Date of receipt of the record copy by the International Bureau : 10 August 1998 (10.08.98)

List of designated Offices

- EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
- EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
- National : AU, BG, BR, CA, CN, CZ, HU, ID, IL, JP, KR, MX, NO, NZ, PL, RO, SG, SI, UA, US

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase
- confirmation of precautionary designations
- requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer:</p> <p>Eugénia Santos</p> <p>Telephone No. (41-22) 338.83.38</p>
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INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

MAZZINI, Giuseppe
 Pharmacia & Upjohn S.p.A.
 Viale Pasteur, 10
 I-20014 Nerviano
 ITALIE

Date of mailing (day/month/year) 13 August 1998 (13.08.98)	
Applicant's or agent's file reference PHA 1776	IMPORTANT NOTIFICATION
International application No. PCT/EP98/04219	International filing date (day/month/year) 02 July 1998 (02.07.98)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 21 July 1997 (21.07.97)
Applicant PHARMACIA & UPJOHN AB et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
21 July 1997 (21.07.97)	60/053,211	US	10 Augu 1998 (10.08.98)
14 Nove 1997 (14.11.97)	9704170-1	SE	10 Augu 1998 (10.08.98)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Eugénia Santos
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.88